Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Thrombus Burden and Outcomes in Patients With COVID-19 Presenting With STEMI Across the Pandemic

Krishnaraj S. Rathod, MD, PhD,[a,b] Zhi Teoh, MD,[a] Angelos Tyrlis, MD,[a] Fizzah A. Choudry, MD, PhD,[a] Stephen M. Hamshere, MD,[a] Katrina Comer, BSc,[a] Oliver Guttmann, MD,[a] Ajay K. Jain, MD,[a] Muhiddin A. Ozkor, MD,[a] Andrew Wragg, PhD,[a] R. Andrew Archbold, MD,[a] Andreas Baumbach, MD, PhD,[a,b] Anthony Mathur, MD, PhD,[a,b] Daniel A. Jones, MD, PhD[a,b]

ABSTRACT

BACKGROUND It has been previously reported during the first COVID-19 outbreak that patients presenting with ST-segment elevation myocardial infarction (STEMI) and concurrent COVID-19 infection have increased thrombus burden and poorer outcomes. To date, there have been no reports comparing the outcomes of COVID-19–positive STEMI patients across all waves of the pandemic.

OBJECTIVES This study compared the baseline demographic, procedural, and angiographic characteristics alongside the clinical outcomes of patients presenting with STEMI and concurrent COVID-19 infection across the COVID-19 pandemic in the United Kingdom.

METHODS This was a single-center, observational study of 1,269 consecutive patients admitted with confirmed STEMI treated with percutaneous coronary intervention (between January 3, 2020 and October 3, 2022). COVID-19–positive patients were split into 3 groups based upon the time course of the pandemic, and a comparison was made between waves.

RESULTS A total of 154 COVID-19–positive patients with STEMI were included in the present analysis and were compared with 1,115 COVID-19–negative patients. Early during the pandemic (wave 1), STEMI patients presenting with concurrent COVID-19 infection had high rates of cardiac arrest, evidence of increased thrombus burden, bigger infarcts, and worse outcomes. However, by wave 3, no differences existed in outcomes between COVID-19–positive and –negative patients, with significant differences compared with earlier COVID-19–positive patients. Poor outcomes later in the study period were predominantly in unvaccinated individuals.

CONCLUSIONS Significant changes have occurred in the clinical characteristics, angiographic features, and outcomes of STEMI patients with COVID-19 infection treated by primary percutaneous coronary intervention during the course of the pandemic. Importantly, outcomes of recent waves and in vaccinated individuals are no different to a non–COVID-19 population. (J Am Coll Cardiol 2023;81:2406–2416) © 2023 by the American College of Cardiology Foundation.

SARS-CoV-2 virus predominantly causes respiratory illness; however, cardiovascular complications, such as myocardial injury, arrhythmias, acute heart failure, and venous thromboembolism, all occur more frequently than previously suspected. Several studies have demonstrated that SARS-CoV-2 infection is associated with increased platelet aggregability and the release of both proinflammatory cytokines and procoagulation factors, resulting in a prothrombotic state.[1,2] As a result, patients with

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From the [a]Department of Cardiology, Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom; and the [b]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom.

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concurrent COVID-19 infection are predisposed to thrombotic disease, both in the venous and arterial circulations.[3] The mechanisms underlying arterial thrombosis in COVID-19, however, remain unclear. Endothelial dysfunction is thought to play a major role[4] ether by direct invasion of the virus[5] or by initiation of a potent cytokine storm.[6] What ensues leads to the recruitment of leukocytes, platelet activation, and induction of extracellular traps,[7] which could contribute to destabilization of coronary plaque. It was previously reported during the first COVID-19 outbreak that patients presenting with ST-segment elevation myocardial infarction (STEMI) and concurrent COVID-19 infection have increased thrombus burden and poorer outcomes.[8]

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However, since then, there have been multiple further waves of the COVID-19 pandemic and the emergence of at least 2 new COVID-19 variants as well as the implementation of vaccination programs. The alpha variant caused a substantial wave of cases in Europe in early 2021, and the delta variant emerged in May 2021 and was the predominant variant for much of the remainder of 2021 until December 2021, with the emergence of the omicron variant. In the United Kingdom, vaccine roll-out started in December 2020 after the first wave, with the elderly being vaccinated first and the majority of the population offered their first doses of vaccinations by mid-2021. There has been emerging data showing fewer hospitalizations and decreased mortality rates in patients, particularly with the omicron variant, despite its increased transmissibility compared with previous variants.[9-11]

Understanding the natural history and treatment responses of patients with STEMI and concurrent COVID-19 infection is vital to determining patient management, particularly in estimating the risk of stent thrombosis and the need for more aggressive antithrombotic agents. This presents a dilemma for clinicians with varying spectrum of clinical practices because of the lack of data in this patient population. To date, there have been no contemporary reports comparing the effect of different COVID-19 variants on thrombus burden and associated outcomes in patients with STEMI. Here, we compare the demographic, procedural, and angiographic characteristics, particularly thrombus burden, alongside the clinical outcomes of consecutive patients presenting to our center with STEMI and concurrent COVID-19 infection across the 3 waves of outbreak in the United Kingdom.

METHODS

STUDY DESIGN AND PATIENT POPULATION. This was a single-center observational study of 1,269 patients admitted with confirmed STEMI treated with primary percutaneous coronary intervention (PCI) at Barts Heart Centre between January 3, 2020 and October 3, 2022. This study was designed to compare characteristics of COVID-19-positive STEMI patients with a control group of COVID-19-negative patients treated during the same timeframe. The United Kingdom experienced significant morbidity and mortality and a disruption to daily life as a result of COVID-19 during 2020 to 2022. The first national lockdown occurred on March 23, 2020, and continued in its most severe form until June 1, 2020 (the first wave). A more transmissible and deadly UK-specific variant (B.1.1.7, World Health Organization name "alpha") was identified in September 2020, and triggered a sharp rise in hospital admissions and deaths, culminating in a second national lockdown during December 2020 to April 2021 (second wave). Measures were relaxed following a reduction in hospital admissions and deaths, until the identification of another more transmissible variant in November 2021 (B.1.1.529, omicron). This resulted in a further peak in hospital admissions during November 2021 to March 2022 (third wave). For the purposes of this study, COVID-19-positive patients were split into 3 groups based upon the time course of the pandemic (wave 1: March 2020 to June 2020; wave 2: September 2020 to March 2021; and wave 3: November 2021 to March 2022). Their baseline characteristics and angiographic, procedural, and clinical outcomes were compared with STEMI patients who were COVID-negative. Patients were included if they were admitted to Barts Heart Centre via the London Ambulance Service either directly from home or via partner district hospitals with cardiac chest pain and STEMI (ST-segment elevation in 2 or more contiguous leads ≥0.2 mV) on their electrocardiogram, or patients admitted with an out of hospital cardiac arrest and electrocardiogram meeting diagnostic criteria for STEMI after the return of spontaneous circulation. Angiographic confirmation of occlusive coronary disease was performed in all cases. Patients with out of hospital cardiac arrest who did not achieve return of spontaneous circulation and those with non-STEMI were excluded from the study.

INTERVENTIONAL PROCEDURES. Full personal protective equipment was worn by all health care professionals involved in each of the procedures; this

ABBREVIATIONS AND ACRONYMS

ACT = activated clotting time

GP = glycoprotein

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

was hospital policy for all STEMI cases during the study period. The interventional strategy was at the discretion of the operator, including the use of direct stenting, predilatation/postdilatation, aspiration thrombectomy, and treatment of bystander noninfarct-related artery stenoses. All patients received a loading dose of aspirin 300 mg and either clopidogrel 600 mg or ticagrelor 180 mg before the procedure. All patients then received aspirin 75 mg/d plus either clopidogrel 75 mg/d or ticagrelor 90 mg twice-daily maintenance therapy. During primary PCI, unfractionated heparin was administered in a loading dose of 70 to 100 U/kg with the activated clotting time (ACT) maintained >250 seconds. ACTs were recorded at 10- to 15-minute intervals after the initial dose of heparin. Glycoprotein (GP) IIb/IIIa inhibitors were used at the operator's discretion and according to local guidelines.

INVESTIGATIONS. All patients with STEMI had baseline serological samples before cardiac catheterization for full blood count, renal and liver function tests, C-reactive protein, D-dimer, fibrinogen, clotting, ferritin, lactate dehydrogenase, ferritin, creatine kinase, and high-sensitivity troponin T. Post-catheterization, all patients underwent routine nasal/pharyngeal swab for the SARS-CoV-2 virus using real time-polymerase chain reaction irrespective of symptoms. Patients with COVID-19 had a confirmed diagnosis based on the identification of SARS-CoV-2 on nasal/pharyngeal swab. All of these patients were managed as COVID-19 positive as per center policy.

DATA COLLECTION. The following data fields were collected as part of our center's routine practice for the British Cardiovascular Intervention Society audit submissions including patient age, sex, ethnicity, height, weight, cardiovascular risk factors, time of symptom onset, and time of arrival at primary PCI hospital. In addition, the following procedure-related data were collected prospectively: target vessel; number of diseased vessels; use of diagnostic devices such as intravascular ultrasound, optical coherence tomography (OCT), or pressure wire; use of aspiration thrombectomy; postdilatation; and use of GP IIb/IIIa inhibitor. Data regarding intraprocedural anticoagulant use and ACTs were collected from patient records with data collectors blinded to patients' COVID-19 status.

ETHICS. The study was registered as a clinical audit with the Barts Quality and Safety Board. The study protocols were approved by the Barts Heart Centre Board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All data was anonymized with removal of patient identifiers prior to analysis.

ENDPOINTS. The primary endpoint was all-cause in-hospital mortality. Secondary endpoints included thrombus burden, Thrombolysis In Myocardial Infarction (TIMI) flow, myocardial blush grade, length of hospitalization and the need for intensive care unit (ICU) admission. Two experienced interventional cardiologists (S.H. and F.C.) blinded to patient COVID-19 status reviewed cine-angiographic images of all patients and scored pre- and post-PCI TIMI flow in the infarct-related artery, thrombus burden pre- and post-PCI (modified thrombus grade for grade 5 thrombus post-initial balloon inflation),[12] and myocardial blush grade.[13] Both reviewers were blinded to clinical outcomes and consensus was achieved in all patients. A proportion (20%) of the films were randomly selected and reanalyzed by the same analysts for intraobserver variability, and by a third experienced interventional cardiologist (O.G.) for interobserver variability of the modified thrombus grade.

STATISTICAL ANALYSIS. Descriptive statistical analyses were performed using SPSS Statistics version 25.0 (IBM). A 2-sided P value <0.05 defined statistical significance. Variables are expressed as counts (percentages), mean ± SD, and median (lower to upper quartile) (ie, for skewed variables) as appropriate. Chi-square analysis or Fisher exact test was used to compare categorical data between groups. Comparisons between waves and COVID-19 status were made using 2-way ANOVA for continuous variables (modified thrombus grade). Correlation was performed using Pearson's correlation analysis for association between heparin and ACT. Binary regression was used with modified thrombus burden (grade 4-5) as an independent predictor of outcome (which incorporated all of the important variables into a model including COVID status, individual waves, and vaccination status). Both a univariate and multivariate model were created

RESULTS

The study population consisted of 154 COVID-19-positive patients with STEMI (first wave: n = 39; second wave: n = 60; and third wave: n = 55) were included in the present analysis and were compared with 1,115 COVID-19-negative patients.

PATIENT CHARACTERISTICS. Patients presenting with concurrent COVID-19 infection from the first 2 waves were more likely than non-COVID-19 patients to be older, women, and from Black, Asian, and minority ethnicity groups (Table 1). Patients in the first wave were also more likely than non-COVID-19 patients and from subsequent waves to be from a higher-risk population (higher incidence of diabetes,

TABLE 1 Baseline Patient Characteristics

	Non-COVID-19 Wave 1 (n = 195)	COVID-19 Wave 1 (n = 39)	*P* Value	Non-COVID-19 Wave 2 (n = 225)	COVID-19 Wave 2 (n = 60)	*P* Value	Non-COVID-19 Wave 3 (n = 695)	COVID-19 Wave 3 (n = 55)	*P* Value	2-Way ANOVA
Age, y	56.1 ± 14.9	61.7 ± 11.0	<0.0001	58.6 ± 12.2	62.7 ± 14.5	0.001	57.3 ± 11.8	58.5 ± 12.7	0.0019	<0.0001
Male	174 (89.2)	33 (84.6)	0.0012	201 (89.3)	44 (73.3)	<0.0001	612 (88.1)	49 (89.1)	0.210	<0.0001
Black, Asian, minority ethnicity	95 (48.7)	22 (56.4)	0.0034	116 (51.6)	28 (46.7)	0.119	341 (49.9)	26 (47.3)	0.099	<0.0001
Body mass index, kg/m^2	27.52 (24.9-28.1)	26.7 (24.8-30.7)	0.121	28.65 (23.8-27.9)	27.55 (24.2-29.4)	0.294	27.91 (25.1-28.0)	26.1 (24.8-27.7)	0.281	<0.0001
Past medical history										<0.0001
Hypertension	95 (48.7)	28 (71.8)	<0.0001	105 (46.7)	26 (43.3)	0.476	326 (46.9)	25 (45.5)	0.623	<0.0001
Hypercholesterolemia	82 (42.1)	24 (61.6)	<0.0001	96 (42.7)	33 (55.0)	0.002	289 (41.6)	22 (40.0)	0.388	<0.0001
Diabetes mellitus	63 (32.3)	18 (46.2)	<0.0001	70 (31.1)	22 (36.7)	0.165	227 (32.7)	14 (25.5)	0.0043	<0.0001
Smoking history	118 (60.1)	24 (61.6)	0.687	121 (53.8)	28 (47.7)	0.0043	400 (57.6)	28 (50.9)	0.098	<0.0001
Previous myocardial infarction	33 (16.9)	6 (15.4)	0.203	37 (16.4)	12 (20.0)	0.0017	119 (17.1)	8 (14.5)	0.039	<0.0001
Previous PCI	30 (15.4)	9 (23.1)	<0.0001	36 (16)	11 (18.3)	0.104	112 (16.1)	6 (10.9)	0.043	<0.0001
STEMI presentation										
Chest pain to reperfusion time, h	6 (3-7)	6 (3-7)	0.463	4 (2-4)	4 (2-6)	0.243	4 (2-4)	4 (2-5)	0.398	0.210
Cardiac arrest	22 (11.3)	11 (28.2)	<0.0001	24 (10.7)	10 (16.7)	0.0237	69 (9.9)	6 (10.9)	0.721	<0.0001
Cardiogenic shock	19 (9.7)	6 (15.4)	0.0023	22 (9.8)	7 (11.7)	0.312	68 (9.8)	6 (10.9)	0.341	<0.0001
Intubated	14 (7.2)	5 (12.8)	<0.0001	12 (5.3)	6 (11.7)	0.0051	56 (8.1)	3 (5.5)	0.023	<0.0001
Laboratory values										
Troponin T, ng/L	311 (105-1,988)	1,221 (179-4,143)	<0.0001	335 (125-959)	639 (173-1,629)	<0.0001	325 (210-620)	403 (42-1,200)	0.073	<0.0001
White cell count, × 10^9/L	12.0 (9.4-14.3)	12.9 (10.6-16.4)	0.332	12.5 (10.1-14.5)	10.9 (9.3-13.9)	0.134	13.1 (10.8-13.9)	10.6 (8.8-12.4)	0.198	<0.0001
Lymphocyte count × 10^9/L	1.6 (1.3-2.1)	1.3 (0.7-2.0)		1.7 (1.4-1.9)	1.4 (1.0-1.7)	0.590	1.6 (1.3-1.8)	1.7 (1.2-1.9)	0.105	<0.0001
Lactate dehydrogenase, U/L	392.0 (265-866)	553 (340-935)	<0.0001	332 (295-698)	368 (292-518)	0.293	366 (302-474)	239 (227-260)	0.0076	<0.0001
D-dimer, mg/L	0.48 (0.2-1.0)	1.86 (0.98-6.6)	0.0014	0.49 (0.3-0.7)	0.96 (0.32-4.22)	0.0032	0.53 (0.4-0.6)	0.50 (0.33-0.81)	0.871	<0.0001
Fibrinogen, g/L	3.31 (2.94-3.66)	4.26 (3.2-7.3)	0.0018	3.88 (3.10-4.93)	3.78 (2.76-5.18)	0265	3.71 (3.22-3.74)	NA	-	<0.0001
Ferritin, μg/L	186 (125-442)	323 (174-859)	<0.0001	210 (144-413)	199 (129-520)	0.487	196 (139-332)	178 (107-313)	0.672	<0.0001
Creatinine, μmol/L	81 (65-125)	80 (71-118)		85 (71-105)	86 (72-107)	0.326	83 (74-99)	74 (66-95)	0.089	<0.0001
Creatine kinase, U/L	713.6 (258-1,499)	493 (165-1,613)	<0.0001	553.0 (174.6-1,698)	286 (137-914)	<0.0001	671.5 (391-1,100)	171 (110-206)	<0.0001	<0.0001
C-reactive protein, mg/L	8 (4-32)	50 (8-185)	0.0010	11 (6-53)	19.5 (5.8-105)	0.0025	9 (6-25)	15 (3-66)	0.029	<0.0001

Values are mean ± SD, median (IQR), or n (%). The characteristics of patients at baseline are compared between COVID-19 patients and a non-COVID-19 control at each wave. Characteristics are compared across all groups using 2-way analysis of variance or chi-square tests.

PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

hypertension, hyperlipidemia, history of previous MI, and previous PCI). Although the time from symptoms to reperfusion was similar in all waves to non-COVID-19 patients, in the first wave, COVID-19 patients had higher rates of cardiac arrest, cardiogenic shock, and requirement for prehospital intubation. However, these rates declined over time such that by wave 3, rates in COVID-19 patients were similar to the non-COVID-19 cohort. Moreover, STEMI patients from the first wave also demonstrated characteristics of more severe COVID-19 infection based on higher levels of D-dimer, lactate dehydrogenase, fibrinogen, ferritin, and C-reactive protein, but lower lymphocyte counts, with these levels trending more toward the levels of the COVID-19-negative STEMI group with consequent waves.

PROCEDURAL CHARACTERISTICS. All patients underwent a primary PCI procedure in all groups (Table 2). Median door-to-balloon times were within 60 minutes and were similar for all groups. Early during the pandemic (wave 1, 2020), STEMI patients presenting with concurrent COVID-19 infection had higher thrombogenicity with significantly higher rates of multivessel thrombosis and stent thrombosis. Despite similar levels of baseline TIMI flow grade 0/1, over time, the modified thrombus grade post-first device for cases with thrombus grade 5 was significantly different over time ($P = 0.0064$) and related to

TABLE 2 Procedural Characteristics

	Non-COVID-19 Wave 1 (n = 195)	COVID-19 Wave 1 (n = 39)	*P* Value	Non-COVID-19 Wave 2 (n = 225)	COVID-19 Wave 2 (n = 60)	*P* Value	Non-COVID-19 Wave 3 (n = 695)	COVID-19 Wave 3 (n = 55)	*P* Value	2-Way ANOVA[a]
Coronary intervention	194 (99.4)	38 (97.4)	0.865	223 (99.1)	60 (100)	0.987	688 (99.1)	55 (100)	0.890	0.416
Door-to-balloon time, min	53 (42-56)	54 (39-70)	0.698	47 (41-62)	50 (30-85)	0.435	48 (35-65)	49 (43-88)	0.732	0.191
Duration of case, min	51 (36-95)	55 (44-90)	0.516	50 (38-89)	51 (38-79)	0.0892	53 (41-73)	50 (41-86)	0.0892	0.0653
Culprit vessel			<0.0001			<0.0001			<0.0001	<0.0001
LMS	5 (2.6)	2 (5.1)		3 (1.3)	2 (3.3)		13 (1.9)	3 (5.5)		
LAD	75 (38.5)	22 (56.4)		110 (48.9)	27 (45.0)		307 (44.2)	22 (40.0)		
Cx	63 (32.3)	4 (10.3)		46 (20.4)	13 (21.7)		143 (20.6)	7 (12.7)		
RCA	52 (26.7)	10 (25.6)		61 (27.1)	18 (30.0)		232 (33.4)	11 (20.0)		
>1 culprit vessel	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	8 (14.5)		
Multivessel thrombosis	0 (0.0)	7 (17.9)	-	0 (0.0)	1 (1.9)	0.030	0 (0.0)	0 (0.0)	0.030	<0.0001
Stent thrombosis	3 (1.5)	4 (10.3)		3 (1.3)	2 (3.8)	0.041	7 (1.0)	2 (2.5)	0.041	<0.0001
Baseline TIMI flow grade 0-1	164 (84.1)	32 (82.1)	0.0614	191 (84.9)	47 (78.3)	0.057	575 (82.7)	44 (80.0)	0.057	<0.0001
Baseline thrombus grade (4-5)	151 (77.4)	33 (84.6)	0.0865	170 (75.6)	47 (78.3)	<0.0001	536 (77.1)	42 (76.4)	<0.0001	<0.0001
Modified thrombus grade post-first device (only for baseline 5)	131	28	<0.0001	160	44	<0.0001	487	39	<0.0001	<0.0001
0	5 (4.1)	0 (0.0)		7 (4.4)	3 (6.8)		42 (8.6)	2 (5.1)		
1	27 (20.5)	0 (0.0)		27 (16.9)	6 (13.6)		70 (14.4)	6 (15.4)		
2	30 (22.9)	1 (3.6)		31 (19.6)	6 (13.6)		93 (19.1)	7 (17.9)		
3	27 (20.4)	7 (25.0)		36 (22.6)	9 (20.5)		120 (24.7)	10 (25.6)		
4	32 (24.4)	12 (42.9)		41 (25.6)	14 (31.8)		127 (26.1)	11 (28.2)		
5	10 (7.7)	8 (28.6)		12 (7.5)	6 (13.6)		35 (7.2)	3 (7.7)		
Modified thrombus grade 4-5	42 (32.1)	21 (75.0)		53 (33.1)	20 (45.0)		162 (33.3)	14 (35.9)		<0.0001
GP IIb/IIIa inhibitor use	42 (21.5)	23 (59.0)	<0.0001	46 (20.4)	24 (40.0)	<0.0001	158 (22.7)	11 (20.0)	0.340	<0.0001
Aspiration thrombectomy use	21 (10.8)	7 (17.9)	0.650	22 (9.8)	9 (15.0)	<0.0001	72 (10.4)	8 (14.5)	<0.0001	<0.0001
Intravascular Imaging use	40 (20.5)	10 (25.6)	0.344	88 (39.1)	19 (31.7)	0.038	329 (47.3)	22 (40.0)	0.027	0.0045
Total heparin dose, U	9,981 ± 4,123	11,125 ± 3,875	0.0658	10,099 ± 4,873	11,489 ± 4,558	0.261	11,325 ± 4,662	11,472 ± 3,592	0.261	0.0013
Average first ACT	297.4 ± 61.2	270.6 ± 69.5	0.386	299.5 ± 68.1	287 ± 61.4	0.068	299 ± 31.0	292.3 ± 64.4	0.068	<0.035
Total heparin dose per weight, U/kg	132.5 ± 62.3	146.2 ± 43.5	0.061	125.1 ± 75.5	137.8 ± 39.1	<0.0001	134.0 ± 42.8	134.6 ± 38.1	<0.0001	<0.0001
Multivessel PCI	9 (5.1)	8 (20.5)	0.084	14 (6.2)	5 (8.3)	<0.0001	28 (4.1)	3 (5.5)	<0.0001	<0.0001
Post-PCI TIMI flow grade 3	190 (97.4)	35 (89.7)	0.107	219 (97.3)	56 (93.3)	0.008	674 (97.0)	52 (94.5)	0.008	<0.0001
Post-PCI myocardial blush grade 2-3	182 (93.3)	21 (53.8)	0.310	208 (92.4)	42 (70.0)	<0.0001	650 (93.5)	50 (90.9)	<0.0001	<0.0001
LV ejection fraction, %	43 (30-55)	43 (30-50)	0.206	47 (35-55)	45 (40-55)	0.0398	44 (40-55)	48 (42.5-55)	0.0398	<0.0001
ICU admission	12 (6.2)	11 (28.0)	0.082	10 (4.4)	6 (11.7)	<0.0001	45 (6.5)	5 (5.5)	<0.0001	<0.0001

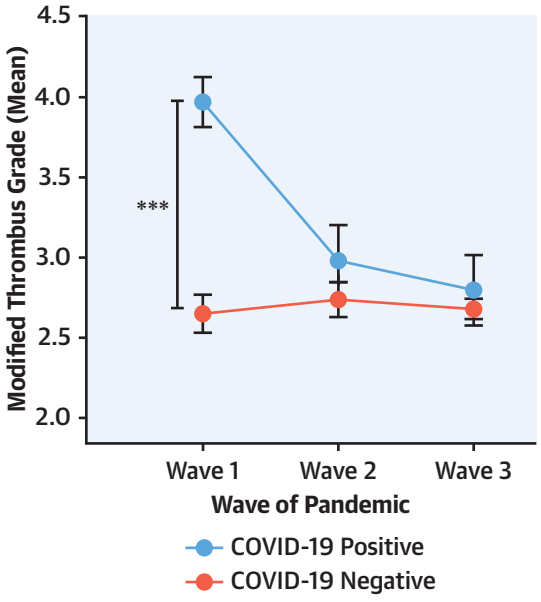
Values are n (%), mean ± SD, median (IQR), or n. The procedural characteristics of patients are compared between COVID-19 patients and a non-COVID-19 control at each wave. Characteristics are compared across all groups using 2-way analysis of variance or chi-square tests. [a]The 2-way analysis of variance is the *P* value for an interaction term in binary logistic regression when the dependent variable is nominal.

ACT = activated clotting time; Cx = circumflex; GP = glycoprotein; ICU = intensive care unit; LAD = left anterior descending; LMS = left main stem; LV = left ventricular; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

COVID status ($P = 0.0001$) (Figure 1). Over time and waves, significantly higher rates were seen in the COVID-19-positive wave 1 group compared with all other COVID-19-positive groups ($P = 0.04$ wave 2 and $P = 0.006$ wave 3). In keeping with this, there was significantly greater use of GP IIb/IIIa inhibitors and aspiration thrombectomy in patients with COVID-19 from the first wave. In addition to TIMI flow grade 3, myocardial blush grade was significantly lower in the COVID-19 group from the first wave compared with the other waves and COVID-19-negative groups. In the first wave, there were 17.9% (n = 7) cases of multivessel coronary thrombosis, of which 6 (15.4%) had no significant evidence of atherosclerotic disease on intravascular imaging (5 OCT, 1 intravascular ultrasound) and were subsequently managed without stent implantation (thrombus aspiration, balloon angioplasty and pharmacotherapy). In wave 2, there was 1.6% (1 case) (again confirmed on OCT); however, no cases were seen in wave 3. No cases occurred in a COVID-19-negative patient.

Looking at predictors of modified thrombus burden, overall COVID-19 status did not predict higher rates of modified thrombus grade following multivariate analysis (OR: 1.3; 95% CI: 0.90-1.80); however, when splitting by wave, wave 1 COVID-19-

FIGURE 1 Modified Thrombus Grade Over Time and COVID-19 Status



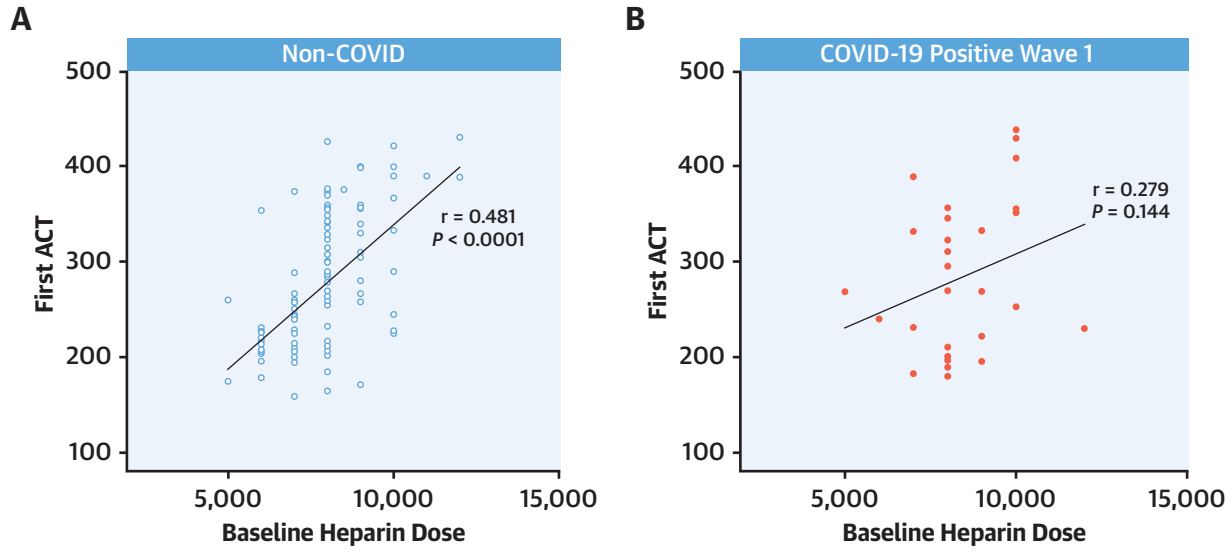
Modified thrombus grade was assessed in all patients with a baseline thrombus grade 5. Data are presented by COVID-19 status and wave. Data expressed as mean ± SEM. ***$P < 0.001$, for 2-way repeated measures analysis of variance.

positive status remained an independent predictor of modified thrombus grade (OR: 1.32; 95% CI: 1.11-1.60) but wave 2 (OR: 1.72; 95% CI: 0.91-1.44) and wave 3 (OR: 1.24; 95% CI: 0.85-1.36) did not.

HEPARIN AND ACT. There were no significant differences across the groups in the total dose of heparin administered ($P = 0.27$), and similar average ACTs were achieved during the procedures ($P = 0.068$). However, the amount of heparin needed per kg was significantly different across the groups, driven by higher doses needed in the wave 1 COVID-19-positive patients. Although first measured ACTs correlated with administered baseline heparin dose in the non-COVID-19 cohort (r = 0.481; $P < 0.0001$), and both wave 2 (r = 0.360; $P = 0.03$) and wave 3 COVID-19-positive patients (r = 0.41; $P = 0.004$), this correlation was not seen in the wave 1 COVID-19-positive group (r = 0.279; $P = 0.144$), suggesting that more heparin was required in the COVID-19 group to achieve similar ACTs. A direct comparison between the waves shows a significant difference between non-COVID-10 and wave 1 COVID-19-positive patients ($P = 0.0301$) but not between the other waves ($P = 0.111$) (Figure 2).

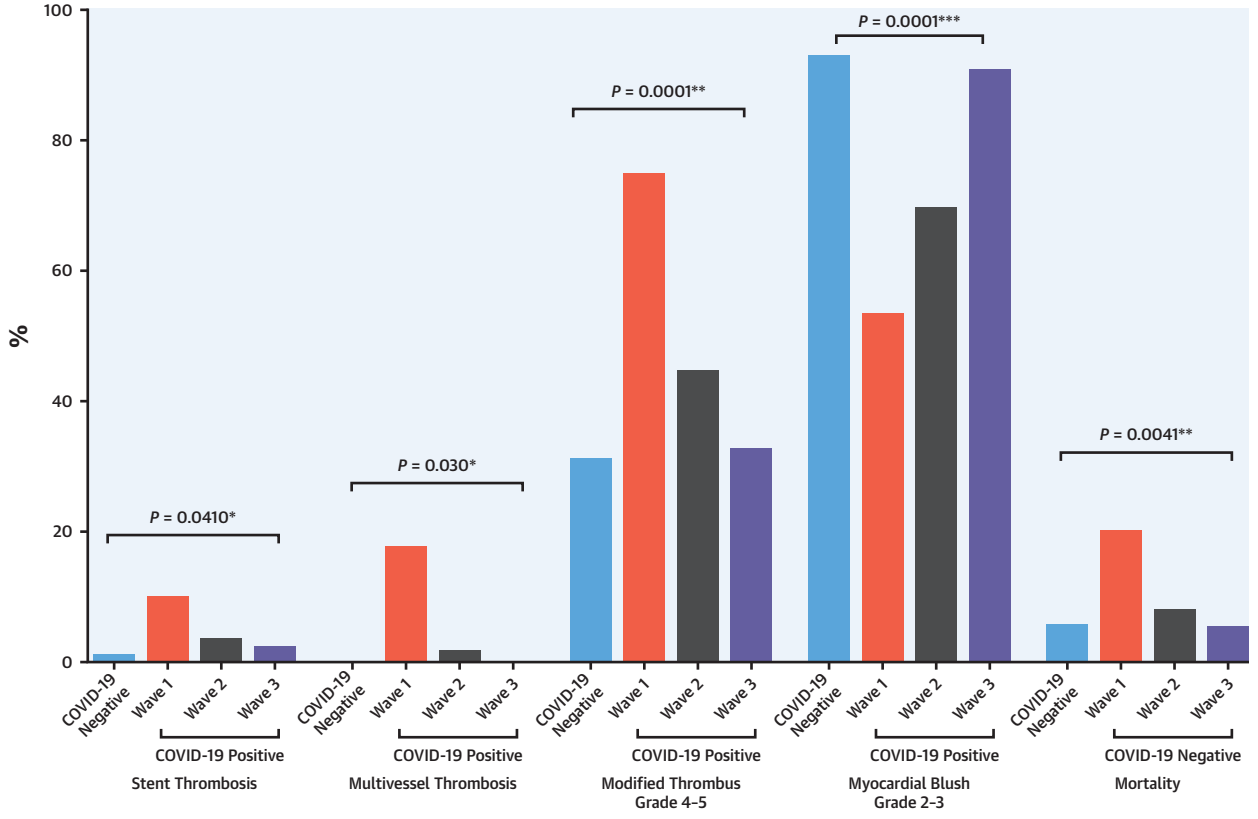
IN-HOSPITAL OUTCOMES. ICU admissions were highest in the wave 1 COVID-19-positive patients (ICU 28.2%) but were similar in the other groups (Figure 2). In COVID-19-positive patients, in-hospital mortality

FIGURE 2 Requirement for Heparin During Primary Percutaneous Coronary Intervention



(A) Correlation between baseline heparin dose and first activated clotting time (ACT) measured after a 10- to 15-min interval in non-COVID-19 patients ($P < 0.0001$). **(B)** Correlation between baseline heparin dose and first ACT measured after a 10- to 15-min interval in COVID-19 wave 1 group ($P = 0.144$).

CENTRAL ILLUSTRATION **Outcomes of ST-Segment Elevation Myocardial Infarction in COVID-19 Infection Across the Pandemic**



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ST-segment elevation myocardial infarction in COVID-19 infection was associated with significantly higher rates of stent thrombosis ($P = 0.0410$), multivessel thrombus ($P = 0.030$), modified thrombus grade 4 to 5 ($P = 0.0008$), lower rates of myocardial blush grade 2 to 3 ($P = 0.0001$), and mortality ($P = 0.0041$) during wave 1 of the pandemic. However, these differences have disappeared over time (vaccinations/strains) *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

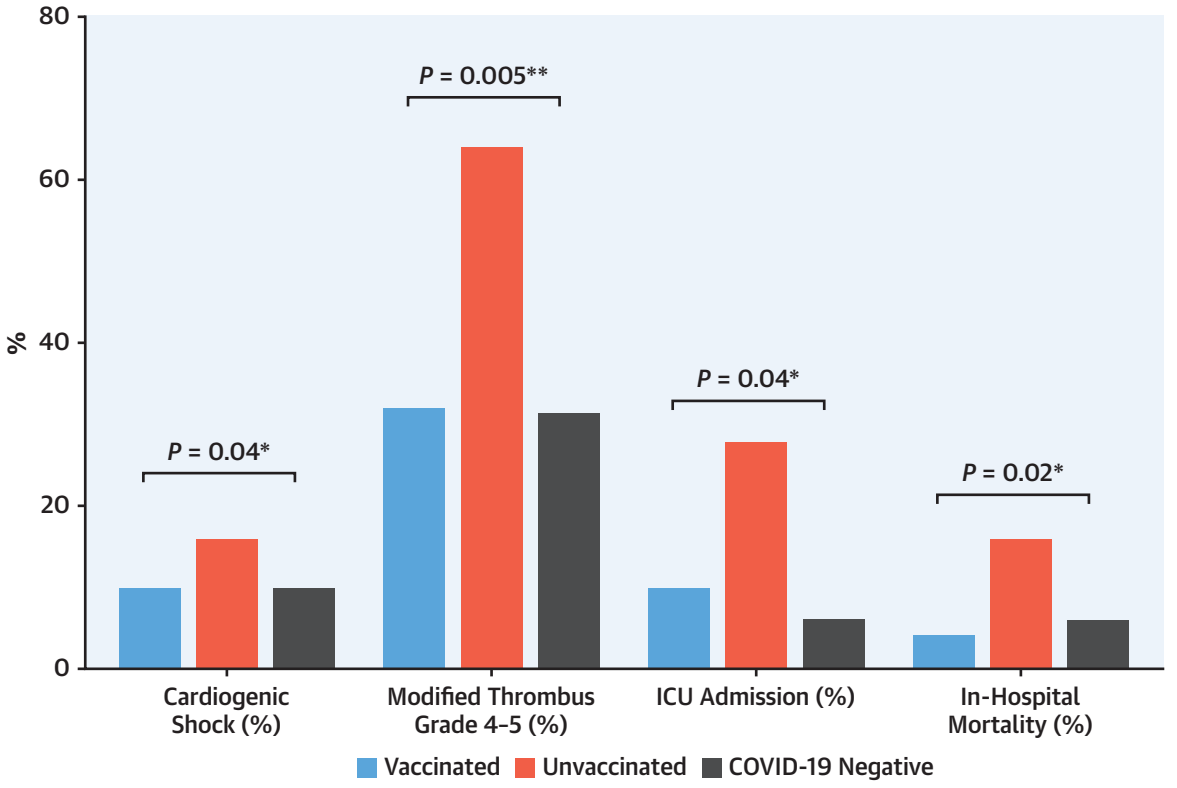
rates declined across the study period with rates of 20.5% in wave 1 compared with 5.7% in wave 3 ($P = 0.036$). No difference in mortality rates existed between wave 3 COVID-19-positive patients and non-COVID-19 patients over the study period (Central Illustration) ($P = 0.754$).

VACCINATION STATUS AND OUTCOME. Overall, there were 66 (42.9%) COVID-19-positive patients who were unvaccinated and 90 who were vaccinated. This consisted of 100% (39 of 39 patients) in wave 1, 31.7% (19 of 60) in wave 2, and 16.4% (9 of 55) in wave 3. Overall, worse outcomes were seen in unvaccinated COVID-19-positive patients compared with both vaccinated COVID-19 patients and non-COVID-19 patients. Unvaccinated COVID-19-positive patients were more likely to present in cardiogenic shock ($P = 0.045$), have a higher thrombus burden ($P = 0.005$), require admission to ICU ($P = 0.044$), and have higher rates of in-hospital mortality ($P = 0.023$) (Figure 3). After adjustment for comorbidities, vaccination status remained an independent predictor of a high thrombus burden (OR: 0.79; 95% CI: 0.41-0.90) (Table 3) but not an adverse outcome (HR: 0.95; 95% CI: 0.74-1.28).

DISCUSSION

To the best of our knowledge, this is the first study to assess comparative data on thrombus burden, management, and outcomes in STEMI patients with concurrent COVID-19 infection during the differing waves of the pandemic, chartering the evolution of COVID-19 variants and vaccination roll-out in the

FIGURE 3 Outcomes Based on Vaccination Status



Unvaccinated COVID-19–positive patients had worse outcomes compared with both vaccinated COVID-19 patients and non–COVID-19 patients. Unvaccinated COVID-19–positive patients were more likely to present in cardiogenic shock ($P = 0.045$), have a higher thrombus burden ($P = 0.005$), require admission to the intensive care unit (ICU) ($P = 0.044$), and have higher rates of in-hospital mortality ($P = 0.023$). *$P < 0.05$. **$P < 0.01$.

TABLE 3 Demonstrating Independent Predictors of Thrombus Using Binary Regression

Modified Thrombus Burden (4-5) Variable	Univariate (95% CI)	*P* Value	Multivariate (95% CI)	*P* Value
Male	1.01 (0.89-1.06)	0.723	Not applicable	Not applicable
Diabetes mellitus	1.03 (0.93-1.21)	0.387	Not applicable	Not applicable
Smoking history	1.11 (0.87-1.36)	0.823	Not applicable	Not applicable
Previous myocardial infarction	1.06 (0.95-1.14)	0.598	Not applicable	Not applicable
Previous PCI	1.03 (0.93-1.27)	0.625	Not applicable	Not applicable
STEMI presentation	1.15 (1.02-1.29)	0.001	Not applicable	Not applicable
Cardiogenic shock	2.90 (1.55-3.32)	0.005	1.20 (1.15-2.65)	0.002
Baseline TIMI flow grade 0-1	2.25 (1.65-2.39)	0.004	1.98 (1.30-2.70)	0.018
Aspiration thrombectomy use	2.19 (0.95-3.99)	0.695	Not applicable	Not applicable
Multivessel PCI	1.10 (0.85-3.19)	0.268	Not applicable	Not applicable
Post-PCI TIMI flow grade 3	0.69 (0.52-0.88)	0.006	0.82 (0.60-0.94)	0.023
LV ejection fraction, >40%	0.19 (0.13-0.24)	0.009	0.87 (0.66-1.42)	0.067
COVID-19 status	1.80 (1.30-2.50)	<0.001	1.30 (0.90-1.80)	0.212
COVID-19–positive wave 1	1.74 (1.47-2.35)	0.021	1.32 (1.11-1.60)	0.038
COVID-19–positive wave 2	1.46 (1.14-1.69)	0.027	1.72 (0.91-1.44)	0.837
COVID-19–positive wave 3	1.34 (1.07-1.55)	0.032	1.24 (0.85-1.36)	0.386
Vaccination status	0.67 (0.52-0.87)	0.014	0.79 (0.41-0.90)	0.027

Abbreviations as in Table 2.

United Kingdom. As previously shown,[8] this analysis demonstrates a clear signal toward negative prognostic outcomes in the first COVID-19 wave with increased thrombus burden (ie, higher rates of multivessel thrombosis, stent thrombosis, higher modified thrombus grade, higher use of GP IIb/IIIa inhibitor and thrombus aspiration and higher weight-adjusted heparin dose to achieve therapeutic ACT) and poorer outcomes (ICU stay, ventilation, mortality). However, there was a clear reduction in mortality across the study period so that waves 2 and 3 were comparable with COVID-19-negative patients. This was in turn associated with reduced thrombus burden and normalization of blood markers of inflammation such as d-dimer. Within waves 2 and 3, poorer outcomes were observed in unvaccinated individuals. Taken together, this data supports the routine management of STEMI in the context of COVID-19 infection with timely primary PCI albeit with specific attention toward thrombus burden and the clear mortality benefit conferred by vaccination and, therefore, its widespread implementation.

Thromboembolic complications have been well-described in the first wave of COVID-19.[1,3,14] COVID-19-positive STEMI patients from the first wave demonstrated higher rates of stent thrombosis[15] with data from our group showing that STEMI in COVID-19 infection is associated with higher thrombotic burden, multivessel thrombosis, stent thrombosis, higher modified thrombus grade, higher use of GP IIb/IIIa inhibitor and thrombus aspiration and higher weight-adjusted heparin dose to achieve therapeutic ACT.[8] This is associated with negative consequences on reperfusion and outcomes, with in-hospital mortality rates in the first wave reported between 18% and 32%.[8,15-17] Although data from our group has demonstrated an 18% in-hospital mortality, other registries have shown higher mortality rates of 23%,[15,16] 29%,[18] and 33%.[17] The recent registry, ISACS-STEMI (Primary Angioplasty for STEMI During COVID-19 Pandemic), reported a significant increase in door-to-balloon and total ischemia times compared with data prepandemic, which may have resulted in this increased mortality,[19] observations confirmed by other studies.[16,20,21] Although, our data comparing COVID-19-positive STEMI patients with the COVID-19-negative control group during the same time period demonstrated poorer outcomes and higher thrombus burden in the first wave despite similar door-to-balloon times.[4]

However, over the study period from March 2020 to March 2022, overall mortality rates from COVID-19 infection in the United Kingdom have fallen with the delta and omicron variants and vaccine roll-out.[22,23] In keeping with this, a recent registry of COVID-19 in STEMI in the United States has demonstrated reduction in mortality and improved outcomes with time.[24] This study is the first to compare angiographic features as well as clinical outcomes across the 3 waves of the pandemic. We show that the differences in clinical characteristics, thrombus burden, and infarct size between COVID-19-positive and -negative patients, although previously present, now no longer remain significantly different with contemporary COVID-19 variants and uptake of vaccination, which may account for the improvement in outcomes seen. Here, our data shows that the differences between COVID-19-positive and -negative groups in characteristics and outcomes seen in the first wave decrease over time with no significant difference seen when comparing wave 3 to the COVID-19-negative population despite no difference in door-to-balloon times seen.

This study shows that COVID-19-positive STEMI patients from wave 1, in line with previous descriptions, were more likely to be older; be women; from Black, Asian, and minority ethnicity groups; and have higher incidence of cardiac risk factors. There were higher rates of cardiac arrest and cardiogenic shock, larger infarcts based on troponin levels, and they have more severe COVID-19 infection based on blood parameters. These differences were incrementally less when comparing waves 2 and 3 with the COVID-19-negative group, with no significant differences seen between wave 3 and COVID-19-negative groups. Thrombogenicity and in-hospital mortality were higher in wave 1, declining in subsequent waves comparable with the COVID-19-negative group. However, unvaccinated individuals overall presented with higher rates of cardiogenic shock, had greater thrombogenicity, and had higher morbidity and mortality. These data indicate that the characteristics and clinical course of a vaccinated COVID-19-positive STEMI patient in 2022 is comparable to non-COVID STEMI groups.

Mechanisms that triggered greater thrombogenicity in STEMI in the first wave of COVID-19 are not known but potentially mediated by endothelial damage, cytokine imbalance, and platelet activation, creating a prothrombotic environment favoring the persistence of intracoronary thrombus, associated with poorer outcomes.[25] The mechanisms underlying the temporal change in COVID-19-positive STEMI may be a combined effect of the protection conferred by vaccination use of steroids and antiviral agents for treatment of hospitalized COVID-19 patients or

mutational changes affecting the behavior of the SARS-CoV-2 virus.

STUDY LIMITATIONS. This is an observational study in a single center and therefore has all the limitations of this type of analysis including bias and the potential for confounding.

CONCLUSIONS

Significant changes have occurred in the clinical characteristics, angiographic features, and outcomes of STEMI patients with COVID-19 infection treated by primary PCI during the course of the pandemic. Our study, although observational, suggests that in the latest wave, vaccinated COVID-19-positive STEMI patients with primary PCI have comparable angiographic features and outcomes to those of COVID-19-negative control subjects, with worse outcomes seen only in the unvaccinated group.

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ADDRESS FOR CORRESPONDENCE: Dr Daniel A. Jones, Barts Heart Centre, St Bartholomews Hospital, West Smithfield, London EC1A 7BE, United Kingdom. E-mail: dan.jones8@nhs.net.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The clinical characteristics, thrombus burden, and outcomes of STEMI in patients with COVID-19 infection varied across the 3 waves of the pandemic. Contemporary outcomes in patients with and without COVID-19 infection are similar except among the unvaccinated.

TRANSLATIONAL OUTLOOK: Efforts are needed to increase awareness that vaccinated COVID-19–positive patients with STEMI can be treated like those who are COVID-19 negative.

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KEY WORDS COVID-19, ECG, PCI, STEMI